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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,234	07/11/2006	Philippe Tessier	6013-129US	4115

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,234	TESSIER ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *9-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060127, 20060330, 20080604*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statements (IDS) filed 27 January 2006, 30 March 2006, and 4 June 2008 have been entered. The Declaration under 37 CFR 1.132 of Philippe A. Tessier submitted on 28 May 2008 is acknowledged. Applicant's amendments of the specification and claims filed on 28 May 2008 have been entered.

Election/Restrictions

Applicant's election of Group I, claims 1-8, in the reply filed on 28 May 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-26 are pending. Claims 9-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-8 are under examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: the filing date for PCT/CA2004/000451 (28 March 2004) is inconsistent to that of the Application Data Sheet (25 March 2004).

"KATZ" Declaration under 37 CFR 1.132 of Philippe A. Tessier

Applicant submits the Declaration under 37 CFR 1.132 of Philippe A. Tessier to declare that the publication by Ryckman et al. (J. Immunol., 2003, Mar. 15, 170(6):3233-3242) emanates from the laboratory of the instant inventor, Philippe A. Tessier, and the other co-inventors named in this patent application. Applicant declares that the subject matter of this reference originates from the present inventors, and that the fifth author of the publication by Rickman et al. (2003) (i.e. Marieve Talbot) was involved in technical aspects of the research and experiments under his supervision and instructions.

In view of the Tessier decalaration, the Ryckman et al. reference cited in the Requirement for Restriction/Election (mailed on 2 May 2008) is no longer qualified for prior art rejection.

Specification

The use of the trademarks, e.g., Trizol, polymyxin B-agarose, Wright-Giemsa, have been noted on page 10, lines 15, 26-27, and page 11, line 10, in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

In addition, the disclosure is objected to because of the following informalities:

There are typographical errors in the specification, e.g., on page 3, line 7; and page 3, line 10 (at the ends of the lines).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for modulating at least one immune cell type in a patient comprising administering to said patient at least one S100 protein or derivatives thereof in an amount sufficient to induce modulation of said cells. The claims encompass a genus of molecules, i.e., S100 proteins or derivatives thereof.

What Applicant has described on pp. 5 of the specification is the S100 protein family which comprises 19 members of small (10 to 14 kDa) acidic calcium-binding proteins. Applicant describes that the myeloid-related proteins (MRP) are a subfamily of S100 proteins, of which, three members have been further characterized, namely S100A8, S100A9 and S100A12, having molecular weight of 10.6, 13.5 and 10.4 kDa respectively, and are expressed abundantly in the cytosol of neutrophils and at lower

levels in monocytes. Applicant describes that S100 proteins generally exist as homodimers (e.g., homodimers of S100A8, S100A9 and S100A12), but some can form heterodimers (e.g., S100A8/A9). Applicant describes that MRPs play a role in the process of neutrophil migration to an inflammatory site. However, Applicant has not provided sufficient written description for the genus, e.g., derivatives of S100 proteins. Even though claims 2 and 5 limit "said S100 protein is a Myeloid Related Protein (MRP)" and "said MRP is S100A8, S100A9, S100A12 or combinations thereof", the claim recitation, however, still encompasses derivatives of these recited S100 protein members. While the prior art (see Zimmer et al., Brain Res. Bull., 1995, 37(4):417-429) teaches the S100 protein family members and the tissue/cell type expression and function of the proteins (see abstract, and pp. 418, Table 1), the prior art, however, does not provide compensatory teachings for the derivatives of the S100 proteins. There is no teaching regarding the identifying characteristics for these molecules, and there is no requirement for these molecules to possess any function/activity. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the conjugation products that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any

combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the S100 protein family members, including three members of the MRP subfamily (namely S100A8, S100A9 and S100A12), but not the full scope of the claimed derivatives, is adequately described in the disclosure.

Claims 1-8 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for stimulating or activating at least one of differentiation, proliferation, or migration of at least one immune cell type in a patient having neutropenia associated with cancer or anti-cancer chemotherapeutic treatment, or a patient having a metastatic cancer or having a skin disease such as a wound, comprising administering to said patient at least one S100 protein selected from the group consisting of S100A8, S100A9 and S100A12 homodimers, and S100A8/A9 heterodimer,

does not reasonably provide enablement for: (1) inhibiting or inactivating (another form of "modulating") the immune cells; (2) using other S100 proteins or derivatives thereof; and (3) administering to any patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The independent claim 1 is directed to a method for modulating at least one immune cell type in a patient comprising administering to said patient at least one S100 protein or derivatives thereof in an amount sufficient to induce modulation of said cells. The claim is broad in that it encompasses or requires the use a genus of molecules, i.e., S100 proteins and derivatives thereof, for treating any patients. What Applicant has disclosed in the specification is a method to stimulate proliferation, differentiation and release of the neutrophils by the use of the S100 protein members, S100A8, S100A9 and S100A12 homodimers, and S100A8/A9 heterodimer. Applicant discloses that administration of S100A8, S100A9 and S100A12 homodomers, as well as S100A8/A9 (heterodimer), led to neutrophil accumulation in blood (Figs. 1 and 2), resulted from an increased neutrophil mobilization from the bone marrow to the blood, and an increased proliferation of neutrophil precursors in the bone marrow (Figs. 3 and 4). Applicant discloses that injection of S100A12 and S100A8/A9 prevented neutropedia induced by anti-cancerous chemotherapy (Fig. 5). Applicant, however, has not provided sufficient support and guidance for using the genus of molecules, i.e., any S100 protein and derivatives thereof. Salama et al. (Eur., J. Surg., Oncol., 2008, 34(4):357-364) recently

reviewed the biological and clinical relevance of the S100 proteins in relation to different tumor types. Salama et al. describes that "[T]here is increasing evidence that altered expression of S100 family members is seen in many cancers including breast, lung, bladder, kidney, thyroid, gastric, prostate and oral cancers. S100 proteins are commonly up-regulated in tumours and this is often associated with tumour progression." Salama et al. states that "Although the precise roles of these proteins in cancer is still to be discovered, many of the family are associated with promoting metastases through interactions with matrix metalloproteinases or by acting as chemoattractants." (see Abstract). Salama et al. points out that some members of the S100 proteins have been documented as tumor suppressors in some cancers but as tumor promoters in others, which demonstrates the complexity of the family and variability of their functions. Since up-regulation of some members of the S100 family would lead to tumor progression, it is obviously not suitable to administer such proteins to a cancer patient.

Further, the claims do not limit the patient population, and therefore, the claims read on treating any disease and in any patient. The specification discloses a method of using S100A8, S100A9 and S100A12 homodimers, and S100A8/A9 heterodimer for stimulating or activating the differentiation, proliferation, or migration of neutrophils in patients having neutropenia, for example, patients undergoing anti-cancer chemotherapeutic treatment. The prior art teaches the use of S100A8/A9 heterodimer for treating wound (e.g., wound healing). The specification, however, does not provide guidance for using the S100 proteins to treat any disease. Because different diseases vary in pathology, causes, and treatment outcomes, without detailed guidance, one

person skilled in the art would need to pick a disease, and determine what the outcome would be. It would require large quantity of experimentation to determine the patient population and treatment outcomes.

Furthermore, the claim language recites “modulating at least one immune cell type”. The word “modulating" encompasses both “stimulating or activating” and “inhibiting or inactivating”. As set forth above, the specification discloses that the S100 proteins can stimulate proliferation of neutrophil precursors in the bone marrow, and stimulate neutrophil mobilization from the bone marrow to the blood. The specification does not teach what immune cell types are inhibited or inactivated. Therefore, the scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to determine if any S100 protein or a derivative thereof can be used for treating a patient with any disease, the lack of direction/guidance presented in the specification regarding the patient populations and treatment regimens, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the complex of different function for different S100 protein members, and many of those are associated with tumor progression, and the breadth of the claims which encompass the use of any S100 protein and encompass treating any patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Devery et al. (J. Immunol., 1994, 152:1888-1897).

The claims are directed to a method for modulating at least one immune cell type in a patient comprising administering to said patient at least one S100 protein or derivatives thereof in an amount sufficient to induce modulation of said cells (claim 1); wherein said modulation is stimulating or activating at least one of differentiation, proliferation, or migration of the immune cells selected from the group consisting of a neutrophil, a monocyte, a macrophage, a platelet, a synoviocyte, a leukocyte and a phagocyte cell (claims 3, 4); wherein said S100 protein is a Myeloid Related Protein (MRP), which is S100A8, S100A9, S100A12 or combinations thereof (claims 2, 5); wherein administering is intravenous, oral, subcutaneous, intramuscular or intraperitoneal administration (claim 8).

Devery et al. teach the use of a S100 protein for activating neutrophils and macrophages *in vivo*. Devery et al. teach that injection of CP-10, as well as MRP-8 (also known as S100A8), into mouse footpad induced accumulation and infiltration of neutrophils and macrophages (pp. 1891, Table 1). Because the specification does not

define for "a patient", given the term its broadest reasonable interpretation, Devery et al. meet this limitation. Therefore, Devery et al. anticipate the instant claims.

Claims 1-5 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Halle et al. (US 2003/0003482 A1, which has a priority filing date on 17 September 2001).

Halle et al. teaches the use of an MRP8/MRP14 heterodimer (MRP8 also known as S100A8, and MRP14 also known as S100A9), or its individual components in combination, for treating and/or preventing skin diseases and wounds in patients, in particular patients with diabetic ulcer which heals poorly [0007]. Halle et al. teaches that the wound healing process includes the temporally consecutive, partially overlapping phases of coagulation, inflammation, proliferation and remodeling, and that in the inflammatory reaction, a variety of cell types, in particular neutrophilic granulocytes and monocytes, migrate into the wound and release mediators of the inflammatory reaction [0002]. Halle et al. also teaches that the routes of administration, e.g., oral, or subcutaneous administration [0059]. Therefore, Halle et al. anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Devery et al.,) as applied to claims 1-5 and 8 above, and further in view of Fidler (Cancer Res., 1985, 45:4714-4726).

Devery et al. teach, as set forth above, that a S100 protein can induce accumulation and infiltration of neutrophils and macrophages. Devery et al., however, do not teach administering the protein to a patient having or having had a cancer (claim 6), or a patient is under or having received chemotherapy treatment (claim 7).

Fidler teaches that activation of macrophages could enhance host destruction of metastasis (pp. 4719, col. 2, section "Destruction of Lung and Lymph Node Metastases by the Systemic Administration of Liposomes Containing Immunomodulators"). Fidler teaches that although the initial results regarding the destruction of metastasis by macrophages are encouraging, it is unlikely that this approach could serve for treatment of large tumors, and that potential therapeutic regimens designed to stimulate host immunity must be used in combination with other treatment modalities such as surgery, chemotherapy, and radiotherapy in order to reduce the tumor burden (pp. 4721, col. 2, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Devery et al., with those of Fidler, to use a S100 protein, such as CP-10 or MRP8, in combination of a chemotherapy, to activate macrophages, and thereby treating metastasis in a cancer patient . One of ordinary skill in the art would have been motivated to do so, because

Devery et al. teach that the S100 protein can induce macrophages *in vivo*, and Fidler teaches that activated macrophages mediate tumor cell destruction, and the therapeutic regimen designed to stimulate macrophages should be used in combination with other treatment modalities, such as chemotherapy. Therefore, the combined teachings provide a reasonable expectation of successfully treating metastatic cancer

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
August 14, 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646